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THE EFFECT OF ANESTHESIA ON ALVEOLAR-OXYGEN DIFFERENCE*

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THE air we breathe contains a nearly constant 21% oxygen, despite impressive attempts to change it by public, private, and industrial waste. At the surface of the mitochondria (where oxygen is used as the final acceptor in the electron transport chain of oxidative phosphorylation) the oxygen tension has been reduced to an equivalent of six tenths of 1%; this represents a drop in partial pressure from 160 to 1 torr.† This loss of pressure results from the alternating steps of convection and diffusion of the oxygen transport system. In the diffusion steps (across the alveolar-capillary membrane and from tissue capillary to intracellular mitochondria) the loss of pressure is the driving

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†A torr is the international unit of pressure equivalent to the pressure exerted by a column of mercury 1 mm. high under an acceleration of 1 gravity at 0° C.

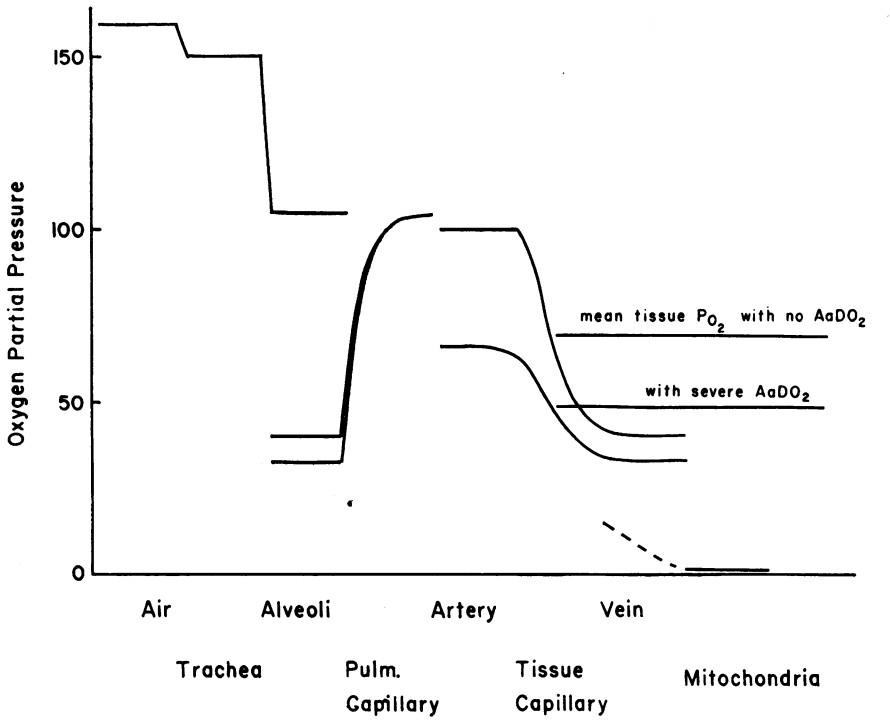

Fig. 1

force for transport of oxygen. In the convection steps (ventilation of lung and circulation of blood) the drop in the partial pressure of oxygen is a measure of inefficiency. For the lung, the measure of inefficiency is the difference in alveolar and arterial oxygen tensions, the alveolar-arterial difference for oxygen, abbreviated AaD O_2.

Ordinarily the lungs work quite efficiently and cause a loss of only 30 to 35% of the available oxygen tension difference between air and mitochondria. The bulk of this drop is a consequence of humidification of inspired gas and of excretion of carbon dioxide. There is rarely more than 5 torr of partial pressure difference for oxygen between the alveolar gas and arterial blood of normal man.

Certain abnormal states, including that of general anesthesia, increase the difference between the oxygen tension of alveolar gas and arterial blood. When breathing air there is very little one can do to increase alveolar oxygen, so that an increase in AaD O_2 necessarily means that the arterial tension falls. Hence tissue oxygen tensions must fall. This is shown schematically in Figure 1 (from suggestions of C. J. Lambert-

TABLE I. THE CAUSES OF AN ALVELOAR-ARTERIAL DIFFERENCE IN GAS TENSION

True venoarterial shunt	Atelectasis
Diffusion block	Diffusion/perfusion maldistribution
Ventilation/perfusion maldistribution	Temporal effects

sen[1]), which shows oxygen tension falling from inspired gas to alveolar gas, arterial blood, capillaries, tissues and, finally, mitochondria. Two different conditions are illustrated: the presence and the absence of an A-a difference.

During anesthesia the patient is not limited to the oxygen content of ordinary air, but can be given either more or less. The borderline potency of nitrous oxide led certain groups of anesthetists in the past to use less than 20% oxygen. The danger of this practice was pointed out by McQuiston, Cullen, and Cook in 1943,[2] who clearly demonstrated that 20% oxygen did not give the usually accepted normal value of 100 torr in arterial blood. Bendixen and his associates have reinforced this concept recently, using more direct measurements of oxygen tension.[3]

Faced with the problem of decreased oxygen tension of arterial blood, the anesthetist has several options, one of which is to increase the inspired oxygen tension, thus restoring or even improving on the oxygen supply to tissue. But if the decrease of oxygen tension is a result of an abnormality or disease, increased inspired oxygen may be only partial treatment. One possibility recognized by Bendixen is atelectasis. High inspired oxygen tension will correct the hypoxemia transiently but at the end of anesthesia may leave the patient prone to postoperative complications such as pneumonia. A program of pulmonary physiotherapy may correct these signs and symptoms but other problems may not be corrected.

THE PHYSIOLOGIC CAUSES OF AaD O_2

Physiologists have explored the AaD O_2 of awake man, in health and disease, and have developed methods which permit subdivisions of the sign of increased AaD O_2 into the components listed in Table I.

Of the cardiac output of normal man 1 to 3% consists of blood from tissue (thus venous blood) which enters the left ventricle and is pumped systemically without having traversed alveolar capillaries. Major components of this anatomic shunt are the Thebesian, bronchial, and pleural

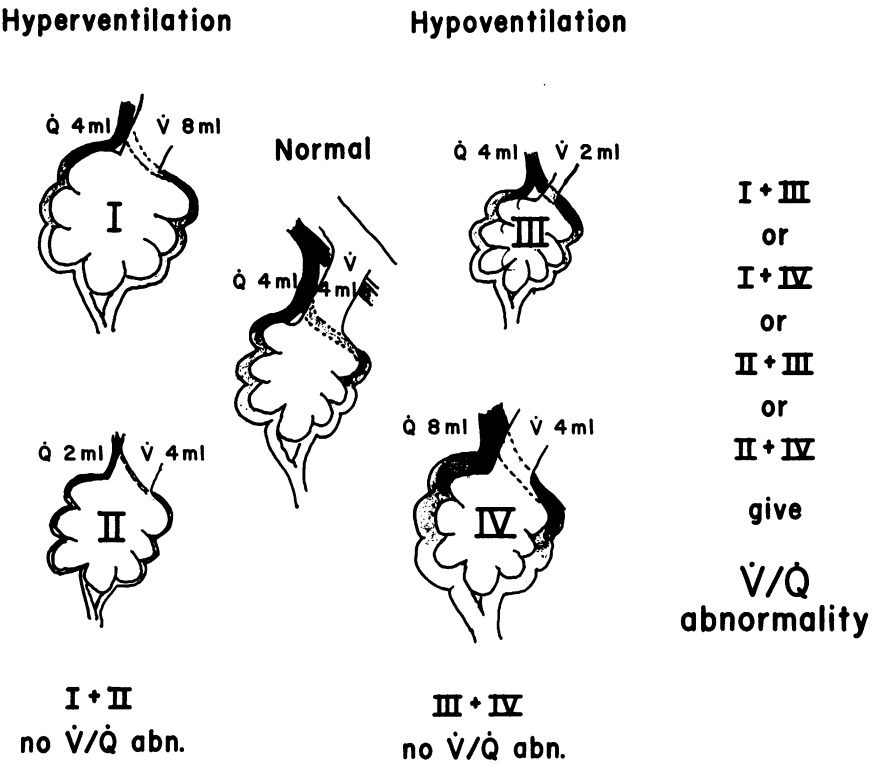

Fig. 2

veins and, possibly, small arteriovenous anastomoses without the lung. Abnormal causes include atrial and ventricular septal defects, and pulmonary A-V fistulae. The true venoarterial or anatomic shunt may be distinguished from the contributions of diffusion block and ventilation/perfusion maldistribution by administering 100% oxygen. In this situation the A-a difference is much increased in magnitude, and the relative contribution of the latter two causes becomes insignificant. This concept is commonly used in clinical medicine to assess the true shunt. It involves the assumption that high oxygen breathing has no pharmacologic action of its own. While this assumption is unsupported, the evidence against it is not impressive and probably should not change the interpretation of the clinical assessment.

A diffusion block as the cause of an A-a difference must be differentiated from the reduction of diffusing capacity caused by the various alveolar capillary block syndromes. The diffusing capacity is based on the average difference of tension along the alveolar capillary between

alveolar gas and blood tension and not that at the end of the capillary. In a group of capillaries with a diffusion block the oxygen tension will rise more slowly than in normal capillaries. But red cells may spend sufficient time in the capillary to become equilibrated with alveolar gas tension before they leave the capillary segment, as is probably the case in most instances of the alveolar-capillary-block syndrome. This is not to deny that such patients have decreased arterial oxygen tension, but the cause for this lower tension should be laid at the door of abnormalities in *distribution* of diffusing capacity, perfusion, and ventilation within the lung.

Ventilation/perfusion maldistribution is the third cause of AaD O_2. The mechanism is a source of some confusion which Figure 2 may help dispel. This figure shows five alveolar units drawn schematically. The normal unit in the center is perfused and ventilated by volumes of blood, Q, and gas, V, which are equal. Units I and II on the left have twice as much ventilation as perfusion, and Unit I has twice as much ventilation as Unit II. Neither of these units singly or together demonstrate a ventilation/perfusion abnormality, but are spoken of as hyperventilated. On the right, Units III and IV have twice as much perfusion as ventilation and are spoken of as hypoventilated units. Taken by themselves either singly or in any combination of such hypoventilated units, no ventilation/perfusion abnormality exists.

When the lung is composed of various units, some of which are hyperventilated and others hypoventilated, *then* a ventilation/perfusion abnormality is said to exist. In normal man there is a regular increase in the ventilation/perfusion ratio from the bottom to the top of man's lung in the erect or sitting position. This ordinarily gives rise to an A-a difference of only three or four torr as calculated by J. B. West.[4] Extensive disease of the lung may cause a depression in arterial PO_2 of as much as 50 torr when breathing air.

Atelectasis is a cause of an arterial alveolar oxygen difference which is functionally identical to true shunt but is differentiated in that it is (in theory at any rate) reversible. Atelectasis is uncommon in normal people except in the presence of an obstructive pulmonary lesion, but it is quite common postoperatively. It will be discussed more fully in a following section.

Another cause of an alveolar-arterial oxygen tension difference is due to the discontinuous nature of respiration, relative to the more nearly

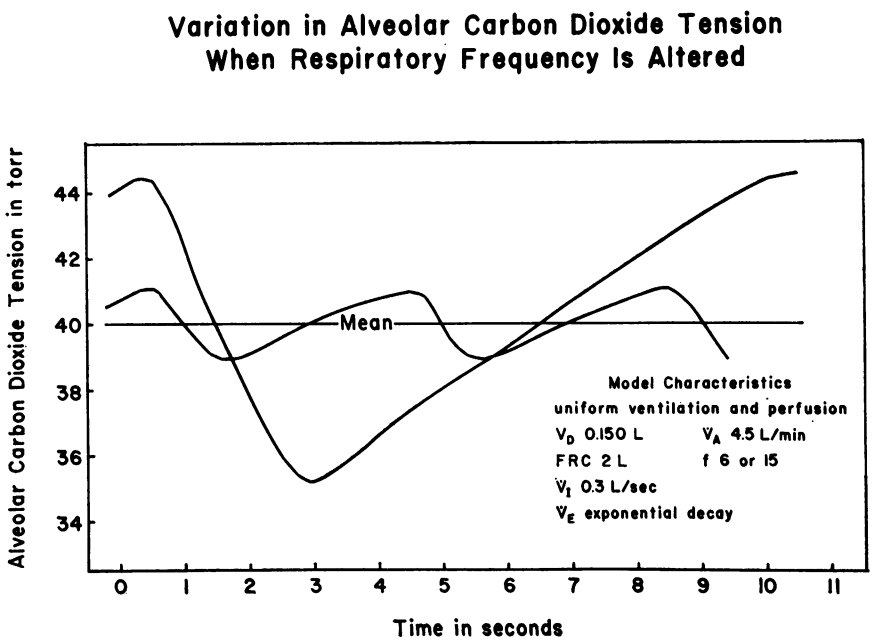

Fig. 3

continuous circulatory processes within the lung, and to the curvilinearity of the hemoglobin dissociation curve. Figure 3 is taken from the work of DuBois and of Rahn, and shows that the oxygen tension within an alveolus varies throughout the respiratory cycle.[5, 6] We cannot sample alveolar oxygen tension directly but must rely on the tracheobronchial tree to conduct a sample of alveolar gas to an accessible site for measurements. We are always looking at oxygen tension delayed somewhat by this transport to the analytic site. There is difficulty identifying just what point is represented in a delivered expired sample. There is also a question as to whether the discontinuous process of respiration has not influenced the transport of blood through the lung by causing cyclic changes in the venous inflow to the heart during respiration. Normally this uncertainty is limited to a few torr or less, but slow frequencies and positive alveolar pressure will certainly increase the uncertainty (as during intermittent positive pressure breathing, for example).

The last cause of A-a differences in man is due to maldistribution of diffusion in respect to perfusion. This is a very difficult topic. Only recently have techniques been developed for investigating it, particu-

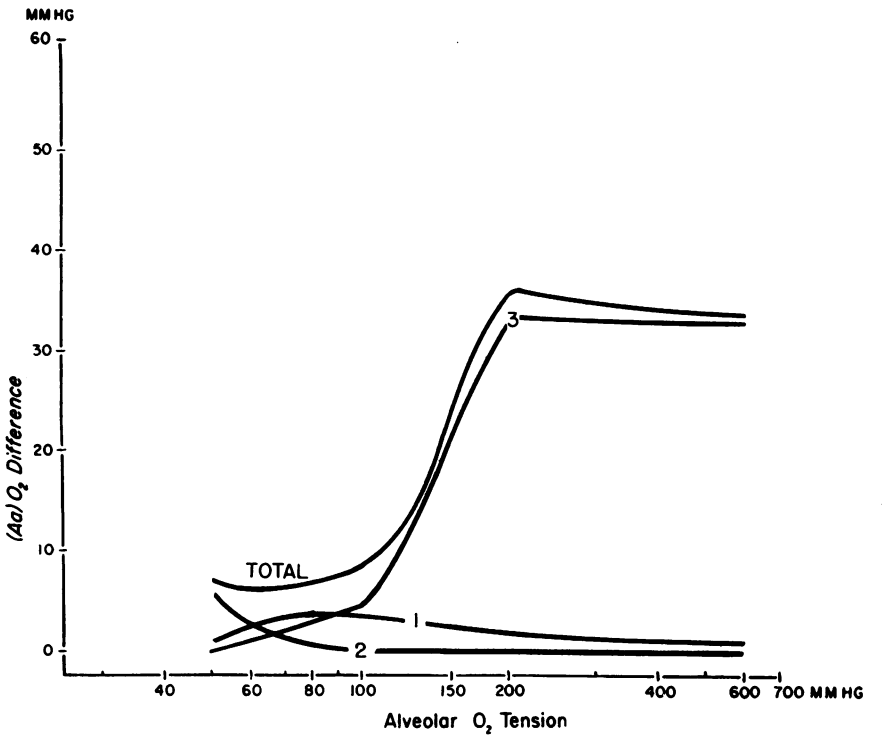

Fig. 4

larly by King and Briscoe.[7] It is included in this discussion for the sake of completeness. There are no measurements available to assess its role in anesthetized man.

To summarize the physiology of the AaD and to show that the causes are separable, Rahn and his colleagues have presented the analysis shown in Figure 4, where the total arterial alveolar oxygen tension difference is plotted as a function of the absolute alveolar oxygen tension (which is in turn related to the inspired tension and to ventilation by the alveolar air equation). Normal man at sea level has an A-a difference near the minimum. As oxygen tensions less than air are breathed the A-a difference due to diffusion arises rapidly. Reilly and his colleagues have taken advantage of this for the measurement of oxygen-diffusing capacity by use of a 12% oxygen mixture. As the oxygen tension of inspired gases increases, the total A-a difference increases rapidly to a plateau above an inspired oxygen concentration of approximately 40%. Diffusion block as a cause has disappeared entirely and the V/Q con-

TABLE II. POSSIBLE CAUSES OF INCREASED AaD O_2 DURING ANESTHESIA

I.	Shunt Contributions
	Increased pulmonary artery pressure
	Increased A-V anastomosis flow
	Increased myocardial oxygen extraction or flow
II.	Atelectasis
	Muscle splinting and decreased tidal volume
	Decreased alveolar stability (surfactant?)
III.	Diffusion Contributions
	Redistribution of pulmonary blood volume
	Redistribution of pulmonary blood flow
IV.	Temporal Contributions
	Varying tidal volume
	Slow or varying respiratory frequency
	An artifact of poorly timed sampling
V.	V/Q Contributions
	Attending altered mechanics
	Attending altered blood distribution
	Attending altered blood *p*H
VI.	Specific Drug Effects
	Pulmonary vasodilators
	Central respiratory depressants

tribution is decreasing as the oxygen tension rises so that the bulk of the A-a difference may be attributed to true venous arterial shunt.

THE PHARMACOLOGY OF THE A-a DIFFERENCE

The process of anesthetization and the use of the various adjuvant drugs in therapies associated with anesthesia, as well as the lethargic postoperative immobility of the patient, all contribute to an increased A-a difference. The A-a difference can be ascribed to one or more of the six physiologic causes discussed above but since the increase is associated with anesthetization, even without an operation, we think of them as pharmacologically induced. The contributions to the increased AaD O_2 are listed in Table II.

Probably the true anatomic shunt is altered only slightly, if at all, by the state of general anesthesia. Possibly an increased pulmonary artery pressure independent of a proportional rise in cardiac output would result in a larger flow through A-V fistulae. There are insufficient reported studies of pulmonary artery catherization during anesthesia to affirm this statement. Preliminary data obtained in our laboratory suggest

that a common moderate increase in pulmonary pressure to the order of 20 to 30% is not uncommon in a healthy man.[8] Also, a marked decrease in myocardial efficiency or an increase in coronary-artery flow, which implies greater oxygen consumption by the myocardium, would increase the A-a difference due to the contribution of Thebesian veins. Since the usual calculation of shunts assumes that all tissues have the same mixed venous oxygen tension, and since we know that myocardial venous tension is regularly below the mixed venous tension of the rest of the body, a small increase in the contribution of the Thebesian veins to the shunt would have a proportionally larger effect on the calculated shunt.

An additional cause of increased arterial-alveolar oxygen difference is a decrease in mixed venous oxygen content, resulting from a disproportionate reduction of cardiac output in relation to body metabolism during anesthesia. Although the magnitude of a calculated physiologic shunt depends only slightly on the arterial venous difference in oxygen content, it is not safe to assume a normal value for this difference in calculating physiologic shunt. A number of investigators have shown, however, that cardiac output at times may be severely reduced by anesthesia. Prys-Roberts *et al.* have even suggested a regular decrease in cardiac output associated with alkalosis during intermittent positive pressure respiration.[9] If body metabolism is relatively unaffected by this alkalosis the Fick principle indicates that the decreased oxygen output is associated with increased arterial-venous content difference and hence with increased calculated shunt for any given value of blood flow through a shunt.

The classical teaching of cardiovascular physiologists requires that pulmonary artery catheters be placed in order to sample true mixed venous blood. This generally requires fluoroscopic control of cardiac catheterization, and it is understandable that not many such values in anesthetized man have been reported. More recently, however, it has become clear that the Cournand type catheter with its relatively rigid curve at the tip has assured that the sampling site was always adjacent to the wall of the chamber in which the catheter lay. Thus a sampling site within the pulmonary artery is demanded in order to insure mixing of venous blood. However, experience with free-floating flexible catheters has shown that mid-right atrium and ventricular sites just within the tricuspid valve will give samples of mixed venous blood indistinguishable from the content of oxygen in the pulmonary artery. Blind cathe-

terization of the right ventricle with soft free-floating catheters is not difficult in the majority of anesthetized patients, so that more data on this point should be forthcoming shortly.

Atelectasis as a cause of an A-a difference is a recently well-publicized concept.[3] The postulated cause of atelectasis is alveolar instability. In a theoretical analysis of the pressure volume curve of a single alveolus Rahn and Farhi showed that at some level below the functional residual capacity the alveolus becomes unstable and snaps suddenly to a nearly collapsed position.[10] Shallow tidal volumes, preferential expansion of certain areas of the lungs (due to the splinting associated with painful incisions), the recumbent position with inactivity—all would predispose to deflation of certain areas to a residual capacity below the functional level. This may result in a diffuse form of alveolar instability. But the classical form of lobar atelectasis is not demonstrable on physical examination or roentgenographic survey.

One of the cures appears to be an increased tidal volume. When tidal volume exceeds 3 ml. per pound of body weight there is a clear-cut improvement in the A-a difference and the rate of change of the A-a difference with time. The cost of increased tidal volumes is an increase in the physiologic dead space which is a form of wasted ventilation. Since ventilation is under the anesthetist's control and the circulation is more difficult to augment, it would seem preferable to pay the price of wasted ventilation in order to compensate for the decreased efficiency of circulation. However, even with a very large tidal volume, the A-a difference during anesthesia exceeds normal values. Other causes for AaD O_2 must be sought, if we are to understand the patient and treat him rationally.

The diffusing capacity of anesthetized man has been measured in only a few circumstances. The actual techniques are poorly explored at present. The measured values for diffusing capacity are somewhat below normally accepted limits.[11, 12] The pulmonary capillary blood volume is slightly reduced. However, calculations based on the cardiac output and volume of blood in the capillaries suggest that a red blood cell spends sufficient time in the capillaries to equilibrate its interior oxygen tension with that of alveolar gas. The subject of diffusion/perfusion distributions and of diffusion/ventilation distributions during anesthesia is completely unexplored. Only a few inferential suggestions are possible. It is unlikely that the state of general anesthesia causes anatomic changes in the alveolar capillary membrane; therefore it is not

likely that the distribution of diffusing capacity per unit volume throughout the lung is altered by anesthesia. If perfusion of the lung is changed by general anesthesia it must necessarily result in a change in the distribution of diffusion to perfusion, thus changing this component of the A-a difference. Further discussion of this point must await techniques for measurement of the distribution of perfusion during anesthesia, and techniques for assessing the maldistribution, if any. However, rather gross limits can be set on the degree of the abnormality and they are insufficient to explain more than a very small fraction of the observed increase in A-a difference during anesthesia.

The problem of temporal maldistribution might actually be improved by the state of general anesthesia insofar as it involves identification of a single portion of the expirate as representative of "ideal alveolar gas." *If* expired gas is sampled through a small-bore high-flow catheter placed in the endotracheal tube near the carina, *if* the measurements are made with a rapidly responding analyzer during controlled or assisted ventilation (when tidal volumes can be augmented sufficiently to assure the washout of dead space between alveoli and the sampling catheter), *if* arterial blood is sampled over a number of respiratory cycles (instead of being drawn rapidly), *if* respiratory cycle frequency is rapid enough, and *if* alveolar oxygen tension is so high that end-capillary oxygen is sufficient at all times to saturate hemoglobin, the A-a difference due to temporal factors becomes insignificantly small. Since all of these factors can be controlled by the anesthetist, a residual A-a difference due to temporal maldistribution can be made insignificantly small. Conversely, very large inflation very slow in frequency or marked variation in tidal volumes (intermittent assistance) can create AaD O_2's.

Ventilation/perfusion maldistribution has recently been investigated during anesthesia by several groups.[8, 13, 14] The differentiation of AaD O_2 as due to ventilation/perfusion, anatomic shunt, or diffusion abnormalities is made by varying the alveolar oxygen tension through changes in the inspired oxygen concentration. When the inspired gas contains more than 40% oxygen the V/Q effect is minimized. A calculation of the shunt from the measured A-a difference is thought to represent the anatomic shunt. When inspired oxygen is in the range of 20 to 25% a measurement of the A-a difference contains both shunt and V/Q elements. When the entire AaD O_2 is thought to be caused by a shunt, it is called the "physiologic shunt." If a measurement of anatomic shunt,

made in the same patient at approximately the same time, is subtracted from the physiologic shunt, the resulting difference is a quantitation of the V/Q maldistribution effect. It must be understood that when 6% of the cardiac output appears to be a shunt, it could be caused by collapse of 6% of a lung the perfusion of which is maintained; it could be due to 60% of the lung being underventilated by 10% with its perfusion maintained; it could be due to an infinite series of combinations of true shunts and of hypoventilated hyperperfused portions. In fact the idea that the lung can be divided into two compartments instead of 300 million (the number of alveoli) is only an abstraction proposed to help understand the abnormality rather than explain its mechanism in detail.

The specific effect of drugs used by anesthetists on the A-a difference is a field of pharmacology as yet only sketchily explored. That oxygen is a drug is perhaps an unfamiliar idea. But oxygen has some rather unexpected properties in concentrations different from the usual 21% in ambient air. Palpitations, anxiety, cyanosis, fear of impending doom, and subsequent lack of consciousness are the well-known effects of hypoxia. When concentrations approaching 100% are inspired, pulmonary vasodilatation, decreased pulmonary ventilation and, eventually, inflammation of the tracheobronchial mucosa result after 12 to 24 hours.

The observations of Nunn and of Bergman that halothane-oxygen anesthesia was associated with large A-a differences attributable to shunt rather than V/Q abnormalities could have been due to a pharmacologic effect of oxygen or of halothane rather than the result of the state of anesthesia. This possibility was tested using nitrous oxide-curare anesthesia and inspired oxygen tensions of 20% and 50%.[15] The thesis that normal tidal volumes of 3 cc. per pound caused a greater AaD O_2 than large tidal volumes of 6 cc. per pound was also tested while total ventilation was unchanged by appropriate variation of the respiratory frequency. These results are shown in Figure 5, where it can be seen that the A-a difference when breathing low oxygen mixtures are similar for normal and large tidal volumes, although increased tenfold above that of normal man. When higher concentrations of oxygen were used there was a significant difference between normal and large tidal volumes. But in both cases the AaD O_2 difference exceeded normal by 2½ and 1½ times respectively. These data indicate that ventilation/perfusion

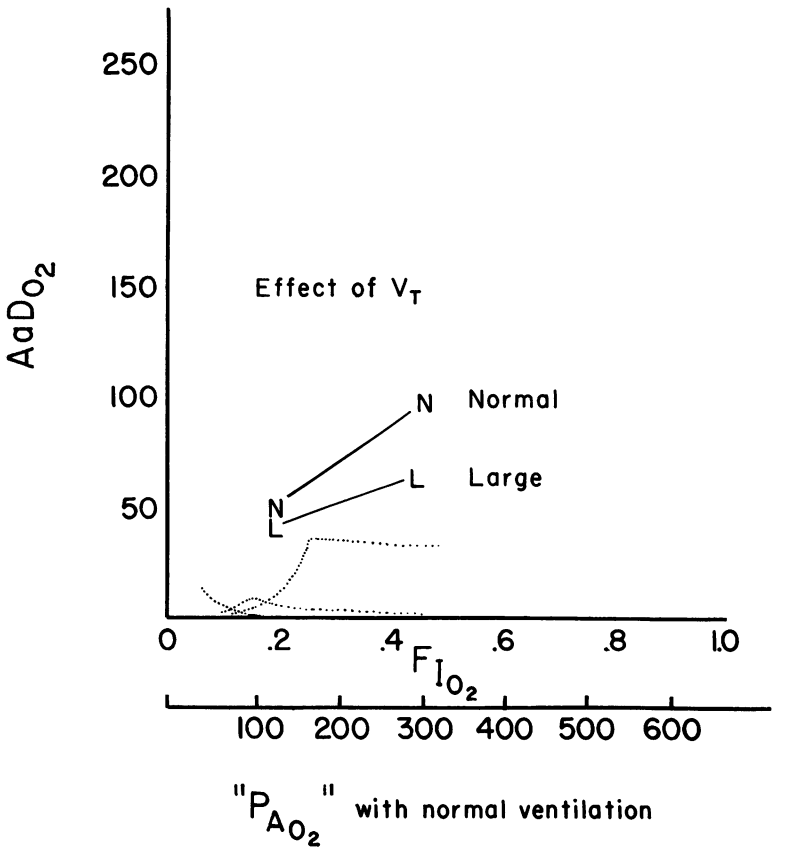

Fig. 5

abnormalities may account for as much as one quarter of the increased physiologic shunt. The bulk of it is still due, however, to the so-called anatomic shunts, which include the possibility of atelectasis. This supports the thesis that 100% oxygen has little if any pharmacologic activity during anesthesia, and the thesis that the state of anesthesia, not a specific anesthetic drug, is causative.

Hyperventilation, as distinct from hyperinflation with each tidal volume, might have deleterious effects on the pulmonary circulation during anesthesia, since alkalosis impairs pulmonary artery constriction.[16] This pharmacologic observation has been supported by the findings of Michenfelder of increased shunting with hyperventilation.[17] This leads to the suggestion that the A-a difference in oxygen might be maximal in the range of 30 torr of arterial PCO_2. When the data of

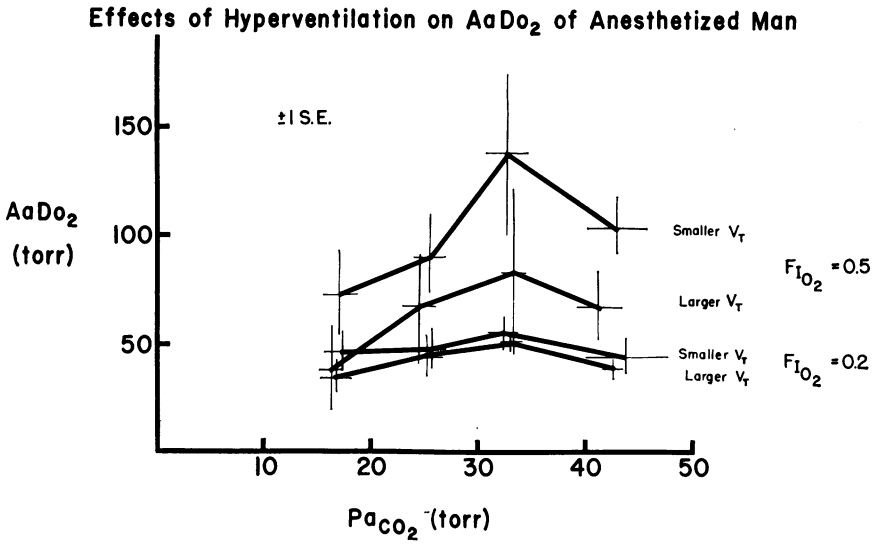

Fig. 6

Figure 5 are arranged in order of increased arterial PCO_2 (Figure 6), support for this suggestion is apparent.

Summary

The oxygen tension in the arterial blood of an anesthetized man is lower than expected from estimations of the alveolar oxygen tension. Thus, although man is well oxygenated while breathing room air awake, he must be given higher concentrations of oxygen when anesthetized. In the usual instances hypoxemia may be avoided by the administration of 25 to 35% of inspired oxygen. However, both intellectual satisfaction and rational therapy in the unusual instances require that we understand the mechanisms causing the increased arterial-alveolar difference for oxygen. We must at least be sure that there are not serious coexisting abnormalities which might be masked rather than remedied by high inspired oxygen tensions.

In awake man the causes of an increased A-a difference for oxygen are primarily true anatomic shunt, ventilation/perfusion abnormality, and diffusion block. Other causes (special cases of the primary three) include atelectasis, diffusion/perfusion distribution abnormalities, and temporal maldistribution. The state of anesthesia and the drugs administered by anesthesiologists do not create new causes for an A-a difference but can be expected to alter the relative magnitude of each of the

effects of pharmacologic activity. Thus mechanisms such as increased pulmonary artery pressure, increased myocardial blood flow, or further desaturation of myocardial blood associated with inefficiency of myocardial contraction during anesthesia, atelectasis due to an abnormal pattern of respiration during anesthesia, and respiratory alkalosis due to augmented ventilation during anesthesia, as well as a greater decrease in cardiac output than in general body metabolism, can contribute to an increased A-a difference during anesthesia. While these causes may be corrected by increased inspired oxygen tension during the anesthesia, they may cause increased postoperative morbidity and mortality if overlooked.

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